EXHIBIT 1

COVINGTON & BURLING

1201 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004-2401
TEL 202.662.6000
FAX 202.662 6291
WWW COV COM

WASHINGTON
NEW YORK
SAN FRANCISCO
LONDON
BRUSSELS

PETER O. SAFIR
TEL 202.662 5162
FAX 202.778 5162
PSAFIR@COV.COM

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BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

Aventis Pharmaceuticals Inc. a member of the sanofi-aventis Group (referred to as 'Aventis') submits this petition under Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA") (21 U.S.C. § 355(j)), 21 C.F.R. §§ 314.94(a)(7), and 21 C.F.R. part 320 to request that the Commissioner of Food and Drugs refuse to approve abbreviated new drug applications ("ANDAs") referencing Arava® (leflunomide) tablets unless the applications (1) contain data from *in vivo* bioequivalence studies confirming that five of their proposed 20 mg leflunomide tablets are bioequivalent to one Arava® 100 mg tablet or (2) seek approval of 100 mg leflunomide tablets that are bioequivalent to 100 mg Arava® tablets.

A. Action Requested

Aventis requests that if an ANDA applicant is not seeking approval of a 100 mg leflunomide tablet that is bioequivalent to Arava® 100 mg tablets, that FDA require the applicant to perform *in vivo* bioequivalence testing to confirm that five of its 20 mg tablets are bioequivalent to one Arava® 100 mg tablet. Aventis further requests that the agency withhold final approval of any ANDA that (1) does not seek approval of a 100 mg leflunomide tablet that is bioequivalent to Arava® 100 mg or (2) does not establish *in vivo* bioequivalence between five 20 mg leflunomide tablets and one Arava® 100 mg tablet.

2005P-0127

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B. Statement of Grounds

I. Background

Aventis holds the new drug application ("NDA") for Arava®.* Arava® is available in 10, 20, and 100 mg tablets. The 100 mg tablet is used for the loading dose that is recommended to initiate Arava® therapy. Specifically, as set forth in the Dosage and Administration section of the approved Arava® package insert ("PI"), [1]

> **Loading Dose**
> Due to the long half-life in patients with RA and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly. It is recommended that ARAVA therapy be initiated with a loading dose of one 100 mg tablet per day for 3 days.

While the Arava® NDA was pending, HMR requested that the use of "5 X 20 mg tablets" be permitted as an alternative to the 100 mg tablet loading dose.[2] FDA denied this request, concluding that the comparative dissolution data was insufficient to support the approval of the alternative dosing regimen.[3] Further FDA stated that it would require a showing of bioequivalence in order to permit five 20 mg Arava® tablets to be used as an alternative to a single 100 mg tablet loading dose.[4]

II. Analysis

On information and belief, FDA has accepted a number of ANDAs seeking approval to market 10 and 20 mg -- but not 100 mg -- generic leflunomide tablets.[5] These applicants, unlike Aventis, would thus have no 100 mg tablet to

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* A predecessor company, Hoechst Marion Roussel, Inc. ("HMR") was the NDA sponsor. Quintiles BRI was HMR's U.S. agent for NDA (No. 20-905).

[1] Package insert for Arava® Tablets (leflunomide). (Tab 1).

[2] NDA 20905, Clinical Pharmacology and Biopharmaceutics Review(s) 2. (Tab 2).

[3] Letter dated June 23, 1998, from Quintiles to Sandra Cook, Project Manager, Division of Anti-Inflammatory, Analgesic, and Opthalmologic Drug Products, FDA. (Tab 3).

[4] Facsimile Transmission dated August 6, 1998 from Sandra Cook at FDA to Joan Bates at Quintiles. (Tab 4).

[5] The analysis that follows does not apply to any ANDA seeking approval of a 100 mg leflunomide tablet that is bioequivalent to Arava® 100mg tablet. Sanofi-aventis does not object to such ANDAs on these grounds.

reference in either the "description," "absorption," or "dosing and administration" sections of their labeling. Aventis believes that these applicants are instead seeking to include a loading dose of five 20 mg leflunomide tablets or seeking to exclude the loading dose altogether. FDA has previously determined, however, that approval of such an alternative loading dose would require additional bioequivalence data not contained in the Arava® NDA. FDA thus cannot approve any ANDA for leflunomide not seeking approval of a 100 mg leflunomide tablet unless it contains *in vivo* bioequivalence data establishing that 5 of the proposed 20 mg leflunomide tablets are bioequivalent to a 100 mg Arava® tablet. Only then could the ANDA product bear the appropriate dosage and administration labeling information -- i.e., instructions to permit the use of five 20 mg tablets as an alternative to the 100 mg Arava® tablet loading dose.

Section 505(j)(2)(A)(v) of the FDCA provides that an ANDA must contain "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under a petition . . . or because the new drug and the listed drugs are produced or distributed by different manufacturers." *See also* 21 CFR § 314.94(a)(8)(iv). Changes in labeling resulting from a difference in manufacturers, however, must not render the proposed generic less safe or effective than the listed drug for the remaining conditions of use. 21 CFR § 314.127(a)(7); *see also* Draft Guidance for Industry: Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications, lines 146-154 (Oct. 2000).

As discussed above, here, the labeling of the reference drug, Arava®, contains important dosage and administration information regarding a 100 mg loading dose. Leflunomide ANDAs must likewise contain such labeling. 21 U.S.C. § 355(j)(2)(A)(v); 21 § CFR 314.94(a)(8)(iv). This information is not the type of information that can be omitted from ANDA labeling simply because the reference drug and the ANDA drug are "produced or distributed by different manufacturers" and the ANDA manufacturer does not make a 100 mg tablet. 21 CFR § 314.127(a)(7).

Rather, omission of the loading dose information may render the generics less effective than Arava®, thereby making the ANDAs unapprovable; the ANDAs would be without the necessary evidence basis to provide for and match the labeling of Arava®. 21 CFR 314.127(a)(7) (ANDA approvable if labeling differences resulting from difference in manufacturer "do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."). Indeed, the three day 100 mg loading dose "is needed to provide steady-state concentration more rapidly" in patients first initiating leflunomide therapy. Although the Arava® PI explains, "[e]limination of the loading dose regimen may decrease the risk of adverse events which may be especially important for some patients at an increased risk of hematologic or hepatic toxicity . . . .;" the three day 100 mg loading dose "is needed to provide steady-state concentration more rapidly" in patients first initiating leflunomide therapy. The Arava® PI explains, "[w]ithout a loading dose, it is

estimated that attainment of steady-state plasma concentrations would require nearly two months of dosing. The resulting plasma concentrations following both loading doses and continued clinical dosing indicate that M1 plasma levels are dose proportional."

The importance of the rapid attainment of steady state plasma levels is supported in the Rheumatoid Arthritis (RA) treatment literature. DMARDs such as Arava should be introduced as soon as possible for the treatment of RA as recommended by treatment guidelines such as "American College of Rheumatology Subcommittee on RA Guidelines, 2002"[6] or the "Management of Early Rheumatoid, A National Clinical Guideline - Scottish Intercollegiate Guidelines Network, 2000."[7]

That erosive changes occur early in the disease, often in the first year,[8] also highlights the importance of an early therapeutic intervention. The initiation of DMARD therapy should not be delayed beyond 3 months for any patient with an established diagnosis who, despite adequate treatment with NSAIDs, has ongoing joint pain, significant morning stiffness or fatigue, active synovitis, persistent elevation of the ESR or CRP level, or radiographic joint damage (Tab 5). Even a brief delay, as little as 8-9 months, in starting DMARD therapy has a significant impact on disease parameters years later.[9,10] Additionally, mortality among RA patients who present early is lower when compared to RA patients who present late in their course of the disease.[11] In consequence, RA should be treated aggressively, as early as possible. Such an approach was proven to be better than the stepwise approach of carefully introducing consecutive

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[6] Guidelines for the Management of Rheumatoid Arthritis. 2002 Update. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Arthritis & Rheum. 2002;46:328-346. (Tab 5).

[7] Management of Early Rheumatoid Arthritis. A National Clinical Guideline. Scottish Intercollegiate Guideline Network. December 2000. (Tab 6).

[8] McGonagle D, Green MJ, Proudman S, Richardson C, Veale D, O'Connor P et al. The majority of patients with rheumatoid arthritis have erosive disease at presentation when magnetic resonance imaging of the dominant hand is employed. Br. J. Rheumatol. 1997;36(Suppl):230. (Tab 7).

[9] Egsmose C, Lund B, Borg G, Petterson H, Berg E, Brodin U, et al. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5-year followup of a prospective double blind placebo controlled study. J. Rheumatol. 1995;22:2208-13. (Tab 8).

[10] Tsakonas E. Fitzgerald AA, Fitzcharles MA, Vividino A, Thorne JC, M'Seffar A, et al. Consequences of the delayed therapy with second-line agents in rheumatoid arthritis: a 3 year followup on the hydroxychloroquine in early rheumatoid arthritis (HERA) study. J. Rheumatol. 2000;27:623-9. (Tab 9).

[11] Symmons DPM, Jones MA, Scott DL, Prior P. Longterm mortality outcome in patients with rheumatoid arthritis: early presenters continue to do well. J. Rheumatol. 1998;25:1072-7. (Tab 10).

DMARDs of increasing potential.[12,13] The general, joint-protecting effect of initiation of intensive, first-line treatment as soon as diagnosis is established was again recently demonstrated in Landewe 2002.[14]

Clinical trials conducted with leflunomide similarly indicated that insufficient treatment already results in significantly more joint damage and irreversible deterioration in physical function after 4 and 6 months, respectively, as evidenced by disease progression in the placebo groups in leflunomide studies US301 and MN301.[15,16,17]

It is consequently important to initiate Arava therapy with a loading dose of one 100 mg tablet per day for 3 days in order to provide steady state concentrations more rapidly and prevent as much as possible a delay in the establishment of an efficient treatment with all the risks associated with this delay.

Leflunomide ANDAs thus cannot be permitted to omit the loading dose information. Nor can ANDAs be permitted to simply substitute "five 20 mg tablets" for the reference to "one 100 mg tablet" in the loading dose section. During its review of the Arava® NDA, FDA determined that additional data would be required to support such alternative dosing information. Accordingly, in order for a generic to obtain approval of a "5 X 20 mg tablet" loading dose in place of the single 100 mg tablet dose,

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[12] Van der Heide A, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma-Frankfort C, van der Veen MJ et al. The Effectiveness of Early Treatment with "Second-Line" Antirheumatic Drugs: a Randomized, Controlled Trial. Ann. Intern. Med. 1996;124:699-707. (Tab 11).

[13] Van Jaarsveld CH, Jacobs JW, van der Veen MJ, Blaauw AA, Kruize AA, Hofman DM et al, on behalf of the Rheumatic Research Foundation Utrecht, The Netherlands. Aggressive treatment in early rheumatoid arthritis: a randomised controlled trial. Ann. Rheum. Dis. 2000;59:468-77. (Tab 12).

[14] Landewé RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, et al. COBRA Combination Therapy in Patients with Early Rheumatoid Arthritis: Long-Term Structural Benefits of a Brief Intervention. Arthritis Rheum 2002;46(2):347-356. (Tab 13).

[15] Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, Loew-Friedrich I, Oed C, Rosenburg R, and the European Leflunomide Study group. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. The Lancet 1999;353:259-266. (Tab 14).

[16] Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, Fox R, Moreland L, Olsen N, Furst D, Caldwell J, Kaine J, Sharp J, Hurley F, Loew-Friedrich I, for the Leflunomide Rheumatoid Arthritis Investigators group. Treatment of Active Rheumatoid Arthritis With Leflunomide Compared With Placebo and Methotrexate. Arch. Intern. Med. 1999;159:2542-2550. (Tab 15).

[17] Strand V. Counterpoint from the trenches: a pragmatic approach to therapeutic trials in rheumatoid arthritis. Arthritis & Rheumatism 2004. (Tab 16).

the applicant must submit data establishing *in vivo* bioequivalence between five of its 20 mg tablets and a single Arava® 100 mg tablet. Without such data an ANDA seeking to substitute a loading dose of five 20 mg tablets would not be approvable. Only with *in vivo* bioequivalence data can a "5 X 20 mg tablets" loading dose be a labeled alternative to the approved Arava® 100 mg tablet loading dose.

III. Conclusion

Aventis respectfully submits that FDA must take the actions requested in this petition to ensure that leflunomide ANDAs contain proper labeling for the safe and effective administration of the drug. Specifically, to ensure that new patients are not put at risk when initiating leflunomide therapy, FDA should not approve a leflunomide ANDA unless (1) it seeks approval of a 100 mg tablet that is bioequivalent to the Arava 100mg loading dose or (2) it contains data establishing *in vivo* bioequivalence between five 20 mg leflunomide tablets and the Arava 100 mg tablet.

C. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R. §§ 25.30 & 25.31.

D. Economic Impact

An economic impact statement will be submitted at the request of the Commissioner.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Peter O. Safir
Kelly A. Falconer
COVINGTON & BURLING
1201 Pennsylvania Avenue, N.W.
P.O. Box 7566
Washington, D.C. 20004-2401
(202) 662-6000

Counsel for Aventis

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